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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,446	04/22/2005	Christoph De Haen	B-0497 PUS	1688

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
10/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,446	DE HAEN ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-22* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 April 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/07/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit II*.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 07/07/2008 in response to the previous Non-Final Office Action (4/10/2008) is acknowledged and has been entered.

Claims 1-10 and 13-22 are pending..

Claims 1-9 and 17-22 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 11 and 13-16 are currently under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 07/07/2008 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections Withdrawn:

The rejection of claims 11, 13-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants amendments..

The rejection of Claim 10 under 35 U.S.C. 102(b) as being anticipated by Hansen et al. (WO 91/04056 A1, 1991, IDS) is withdrawn in view of Applicants amendments. In particular, Hansen et al. teaches that the reducing agent in cysteine, not TCEP as claimed.

Objections Maintained:

The drawings remain objected to under 37 CFR 1.83(a) because they fail to show the migration as described in the specification (page 18, lines 19+). Any structural detail that is essential

for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

In response to this objection, Applicants contend that the objection appears to pertain to Figure 3 since it is the only figure showing changes in migration distance. Hence, Applicants submit that Figure 3 is described at page 18 as cited by the Examiner and explained in detail on page 24 in Example 5, wherein native eletrophoresis was used to show the differences in charge introduced by the DTPA derivative after conjugation with Compound D. For example, Applicants assert that in each case the Fab preparations conjugated with Compound D (lanes 2, 4 and 6) showed the same reduction in migration distance towards the cathode when compared with the corresponding unconjugated Fab preparation (lanes 1, 3 and 5 respectively). Looking at Figure 3, Applicants assert that the shortened migration distance in lanes 2, 4 and 6 is apparent in comparison to Lanes 1, 3 and 5. Thus, Applicants assert that Figure 3 includes all structural details essential for a proper understanding of the invention and is in full compliance with 37 CFR 1.83 (a).

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges and does not dispute Applicants assertions of what Figure 3 is suppose to represent, e.g., a shortened migration distance in lanes 2, 4 and 6 is apparent in comparison to Lanes 1, 3 and 5. However, the Examiner recognizes that Figure 3, filed on 4/22/2005, is extremely vague. For example, while one of skill could possibly make out the

migration in lanes 1 and 3, the "migration" in lanes 2, 4, 5 and 6 cannot be determined. As such, the objection is maintained.

Rejections Maintained, but amended in view of Applicants Amendments:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 13 and 15 remain rejected under 35 U.S.C. 102(b) as being anticipated by Maurer et al. (WO 02/056907 A2, IDS) as evidenced by Cruse and Lewis (Cruse, Julius and Lewis, Robert. Illustrated Dictionary of Immunology Boca Raton, FL, 1995).

Maurer et al. teach a method of coupling Fab fragments to Qβ capsid proteins comprising combining a first solution of a reduced fab fragment generated by reacting a concentration of a Fab fragment, 2.5 mg/mL, at a pH of 7.2 with different concentration (0-1000μM, e.g. 0 mM to 1mM) of either dithiothreitol (DTT) or tricarboxyethylphosphine (TCEP) for 30 minutes at 25°C and a second solution comprising a SMPH derivatized Qβ capsid protein, wherein the final concentration of the protein and Fab were 1.14 mg/mL and 1.78 mg/mL respectively and the reaction proceeded overnight at 25°C (pages 140-141, Example 16). Thus, while Maurer et al. do not explicitly report the Fab concentration in μM or the conjugating moiety concentration in mM, e.g., micromoles/microliter or millimoles/mL, the concentration of the Fab will depend on its molecular weight reported in g/mol which as evidenced by Cruse and Lewis is 47,000 KD, e.g., 47,0000 g/mol (Definition of Fab fragment). Thus, the μM concentration used by the prior art reference is 53μM (See Exhibit I for conversion). In addition, while Maurer et al. do not explicitly report the stoichiometric ratio between the Fab fragment and Qβ capsid protein to be in the range of 1.95 to 2.05, the claimed stiochiometric moar ratio will depend on the molecular weight reported in g/mol which for the reduced Fab fragment is 23,500 Kd and for the protein appears to be about 15,000Kd (see figure 21, marker for Qβ capsid protein. Thus, the stiochiometric ratio used by the prior art is 1

Qβ capsid protein's per 1 Fab fragment (see Exhibit II for conversion). Lastly, although Maurer et al. do not explicitly teach that Qβ capsid protein is a molecular entity which imparts diagnostic utility, the claimed limitation does not appear to result in a manipulative difference between the prior art because the specification teaches that preferred examples of molecular entities having diagnostic or therapeutic utility include, but are not limited to, a hapten recognized by a distinct antibody or fragment thereof (page 11, lines 20-26). Thus, in view of Maurer et al. teaching that the coupled product reacted with a distinct antibody, an anti-Qβ antibody (page 141, 3rd full paragraph), the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure.

In response to this rejection, Applicants contend that the claims, as amended, require a chemical conjugate between a Fab fragment and molecular entities imparting diagnostic utility, wherein the selective and quantitative reduction of the inter-chain disulfide bond of the Fab fragment occurs with TCEP at concentrations ranging from 0.1 mM to 10 mM and wherein the stiochiometric molar ratio of molecular entity to Fab fragment in the conjugates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05. In contrast, Applicants assert that Maurer teaches a method of coupling a Fab fragment to a Qβ caspid protien, e.g., a protein useful for vaccination, but not diagnostically useful. Furthermore, Applicants note that contrary to the Examiner's assertions, Maurer does not teach or suggest use of TCEP in a concentration of 0 to 1000 mM. Rather, Applicants assert that Example 16 of Maurer states that varying the concentration of TCEP or DTT ranging from 0 to 1000 μM.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges Applicants amendments to the claims to a require a chemical conjugate between a Fab fragment and molecular entities imparting diagnostic utility, wherein the selective and quantitative reduction of the inter-chain disulfide bond of the Fab fragment occurs with TCEP at concentrations ranging from 0.1 mM to 10 mM and wherein the stiochiometric molar ratio of molecular entity to Fab fragment in the conjugates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05. However, the Examiner recognizes that there does not appear to be a patentably difference between the claimed method and the method taught by Maurer et al. For example, the specification teaches that preferred examples of molecular entities having diagnostic or therapeutic utility include, but are not limited to, a hapten recognized by a

distinct antibody or fragment thereof (page 11, lines 20-26), wherein a hapten can be defined as a small separable part of an antigen that reacts specifically with an antibody but is incapable of stimulating antibody production except in combination with a carrier protein molecule (see Merriam-Webster on-line dictionary). Thus, in view of Applicants remarks that the protein is useful for vaccination purposes, e.g., antibody production, and Maurer et al.'s teachings that the coupled product reacted with a distinct antibody, an anti-Qβ antibody (page 141, 3rd full paragraph), the Qβ caspid protein appears to be molecular entity which imparts diagnostic utility as defined in the specification, e.g., a hapten. Additionally, with regards to the TCEP concentration, the Examiner acknowledges that Maurer et al. teach that the concentration of TCEP is between 0 to 1000 μM; and further, the Examiner erroneously stated that Maurer et al. taught a TCEP concentration of 0 to 1000 mM (possible key stroke error, e.g, not making the "m" a symbol for micro). However, the Examiner recognizes that 0 to 1000 μM is equivalent to 0 to 1 mM. As such, the concentration of TCEP taught by Maurer et al .still appears to fall within the claimed range.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14 and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al. (WO 02/056907 A2, IDS) as evidenced by Cruse and Lewis (Cruse, Julius and Lewis, Robert. Illustrated Dictionary of Immunology Boca Raton, FL, 1995).

Maurer et al. teach a method of coupling Fab fragments to Qβ capsid proteins comprising combining a first solution of a reduced fab fragment generated by reacting a concentration of a Fab fragment, 2.5 mg/mL, at a pH of 7.2 with different concentration (0-1000μM, e.g. 0 mM to 1mM) of either dithiothreitol (DTT) or tricarboxyethylphosphine (TCEP) for 30 minutes at 25°C and a second solution comprising a SMPH derivatized Qβ capsid protein, wherein the final concentration of the protein and Fab were 1.14 mg/mL and 1.78 mg/mL respectively and the reaction proceeded

overnight at 25°C (pages 140-141, Example 16). Thus, while Maurer et al. do not explicitly report the Fab concentration in μM or the conjugating moiety concentration in mM, e.g., micromoles/microliter or millimoles/mL, the concentration of the Fab will depend on its molecular weight reported in g/mol which as evidenced by Cruse and Lewis is 47,000 KD, e.g., 47,0000 g/mol (Definition of Fab fragment). Thus, the μM concentration used by the prior art reference is 53μM (See Exhibit I for conversion). In addition, while Maurer et al. do not explicitly report the stiochiometric ratio between the Fab fragment and Qβ capsid protein to be in the range of 1.95 to 2.05, the claimed stiochiometric molar ratio will depend on the molecular weight reported in g/mol which for the reduced Fab fragment is 23,5000 Kd and for the protein appears to be about 15,000Kd (see figure 21, marker for Qβ capsid protein. Thus, the stiochiometric ratio used by the prior art is 1 Qβ capsid protein's per 1 Fab fragments (see Exhibit II for conversion). Lastly, although Maurer et al. do not explicitly teach that Qβ capsid protein is a molecular entity which imparts diagnostic utility, the claimed limitation does not appear to result in a manipulative difference between the prior art because the specification teaches that preferred examples of molecular entities having diagnostic or therapeutic utility include, but are not limited to, a hapten recognized by a distinct antibody or fragment thereof (page 11, lines 20-26). Thus, in view of Maurer et al. teaching that the coupled product reacted with a distinct antibody, an anti-Qβ antibody (page 141, 3rd full paragraph), the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure.

Maurer et al. does not explicitly teach that the Fab concentration is from 1.5-10 μM or 1-5 μM. Nor does Maurer et al. explicitly teach that the conjugate moiety concentration is 0.1-100 mM.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the concentration of the Fab fragment and resultant conjugate moiety because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by optimizing the concentration of the Fab fragment and resultant conjugate moiety, one would achieve the optimal reaction conditions for the conjugation.

In response to this rejection, Applicants assert that the combination of the cited references does not teach or suggest of the claim limitations and that the claimed compounds possess unexpectedly superior properties. For example, Applicants assert, as explained supra, Maurer is directed to producing conjugates for vaccines and does not teach or suggest diagnostic conjugates. Additionally, Applicants assert that, unlike Maurer, the present process provides for a diagnostic entity with a controlled stoichiometry of conjugation (e.g., the stiochiometric molar ratio of molecular entity to Fab fragment in the conjugates is in the range from 0.95 to 1.05 or in the range from 1.85 to 2.05). Hence, Applicants contend that being able to control the stiochiometric ratio during conjugation is of the utmost importance as it allows for chemically defined conjugated diagnostic compounds, in comparison to rather complex and poorly defined mixtures of conjugated compounds obtained according to the process of Maurer, wherein each of the conjugates in the obtained mixture may have its own stoichiometry of substitution and thus, the claimed stiochiometric ratios cannot be achieved. Indeed, Applicants assert that Example 16 of Maurer establishes that each of the successful couplings between the fab fragment and the protein (see lanes 5-8 and lanes 10-12 of figure 21) is part of a very complex mixture in which only a portion includes the desired product (with average MW of 40kDa, shown by an arrow in Figure 21). Thus, Applicants assert that due to the inability of the Maurer method to control stoichiometry, extensive, expensive and impractical separation methods must be used to isolate the derivative of interest from the complex mixture containing it. In contrast, Applicants assert that the claimed method unexpectedly yields controlled stiochiometry of substitution through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP at concentrations ranging from 0.1 to 10 mM so as to provide two sulfhydryl groups to be then reacted with the diagnostic moiety or moieties bearing free sulfhydryl reactive groups.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants arguments pertaining to Maurer et al teaching a vaccine not a diagnostic entity, the Examiner acknowledges these assertions. However, the Examiner recognizes that there does not appear to be a patentably difference between the claimed method and the method taught by Maurer et al. For example, the specification teaches that preferred examples of molecular entities having diagnostic or therapeutic utility include, but are not limited to, a hapten recognized by a distinct antibody or fragment thereof (page 11, lines 20-26), wherein a hapten can be

defined as a small separable part of an antigen that reacts specifically with an antibody but is incapable of stimulating antibody production except in combination with a carrier protein molecule (see Merriam-Webster on-line dictionary). Thus, in view of Applicants remarks that the protein is useful for vaccination purposes, e.g., antibody production, and Maurer et al.'s teachings that the coupled product reacted with a distinct antibody, an anti-Qβ antibody (page 141, 3rd full paragraph), the Qβ caspid protein appears to be molecular entity which imparts diagnostic utility as defined in the specification, e.g., a hapten. With regards to Applicants arguments pertaining to the control of the stoichiometry of the reagents, the Examiner acknowledges that the instant claims require that the conjugation stiochiometric molar ratio of molecular entity of Fab fragment is in the range from 0.95 to 1.05 or in the range of 1.95 to 2.05. However, the Examiner recognizes that Maurer et al.'s method of conjugating the protein to the Fab fragment appears to use a controlled stiochiometric molar ratio of 1 to 1, as set forth above (see Exhibit II). Thus, while the Examiner does not dispute that the reaction produces a complex mixture of products and reactants, the Examiner recognizes that the product, e.g., average molecular weight of approximately 40Kd shown by the arrow in Figure 21, is still produced using the method taught by Maurer et al.. Lastly, regarding Applicants arguments pertaining to unexpected results, the Examiner acknowledges Applicants assertions that the claimed method unexpectedly yields controlled stiochiometry of substitution through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP at concentrations ranging from 0.1 to 10 mM so as to provide two sulfhydryl groups to be then reacted with the diagnostic moiety or moieties bearing free sulfhydryl reactive groups. However, the Examiner recognizes that Maurer et al teaches using TCEP in a concentration of 1 mM, which anticipates Applicants claimed concentration of TCEP, e.g., concentration ranging from 0.1 to 10 mM. Accordingly, the mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979).

Therefore, No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Examiner
Art Unit 1642

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